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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/816,465 | 04/01/2004 | Sonia Moreno-Lopez | MORENO-LOPEZ | 8524 |

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| ART UNIT | PAPER NUMBER |
| 1633 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/816,465 | MORENO-LOPEZ ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment and response received on 8/3/09 has been entered. Claims 1-41 are canceled. Claims 42-44 are currently pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

### *Claim Rejections - 35 USC § 103*

The rejection of claims 42 and 44 under 35 U.S.C. 103(a) as being unpatentable over McCluskie et al. (1999) Mol. Med., Vol. 5, 287-300 (IDS of 7/04, ref AU), in view of U.S. Patent No. 6,451,593 (2002), effective filing date of at least May 12, 1999, hereafter referred to as Wittig et al. (previously cited on 892 of 9/22/06), and Makkerh et al. (1996) Current Biology, Vol. 6 (8), 1025-1027, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that McCluskie et al. was previously cited as a reference in an art rejection of the claims in this application and that it was withdrawn because of applicant's arguments in favor of Schirmbeck which is closer prior art. The applicant also states that McCluskie et al. is not relevant because it does not teach the use of a MIDGE vector.

In response, applicant is in error regarding McCluskie et al. The McCluskie et al. reference was never cited in any art rejection, 102 or 103, over any claim ever pending in the instant application prior to the previous office action mailed on 4/9/09 to which applicant is now responding. The citation of McCluskie in a 103 rejection in the previous office action was the first and only time McCluskie et al. has been cited by the examiner in any type of rejection. Thus, applicant's comments about the examiner "taking one more shot" with McCluskie et al. are completely inaccurate. Furthermore, by applicant's characterization of McCluskie et al. as "irrelevant" it is supposed that the applicant is arguing that McCluskie et al. is not analogous art. If this is the case then the applicant is reminded that it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the instant methods are generally drawn to methods of eliciting an immune response in a living being with a genetic vaccine which encodes a hepatitis antigen. McCluskie et al. teaches a genetic vaccine for eliciting Th1 type cellular immune response against hepatitis comprising a plasmid vector encoding a hepatitis antigen and methods of administering the vaccine using intradermal injection to generate hepatitis antigen specific CTL and antibodies (McCluskie et al., pages 289 and 291-294). In particular, McCluskie et al. demonstrates that intradermal injection of plasmid encoding the major surface protein of Hepatitis B envelope protein generates significant CTL responses and predominantly Th1 type antibody responses at 4 weeks post-vaccination (McCluskie et al., pages 291-292, Figures 1 and 2). Thus, McCluskie et al. is clearly in the field of applicant's endeavor and reasonably pertinent

to the particular problem of inducing protective immunity to hepatitis. As such, it is strongly disagreed that McCluskie et al. is irrelevant to the obviousness of the instant claimed methods.

The applicant further argues that that there would be no motivation for a skilled artisan reading McCluskie et al. to look to Wittig et al. without hindsight reasoning, and that McCluskie et al. teaches away from the using the vectors disclosed by Wittig et al. The applicant then argues that the Supreme Court decision in KSR did not negate the requirement for the TSM test, and that there is no teaching, suggestion, or motivation to modify the DNA expression construct of McCluskie et al. More specifically, the applicant argues that McCluskie et al. teaches the administration of plasmid vector vaccines and does not disclose the use of MIDGE vectors. The applicant also states that it was known at the time of filing that plasmid expression vectors have disadvantages as vaccines due to unwanted toxic immunological side effects due to unmethylated CpG sequences in the plasmid, citing a post-filing reference, Darquet et al.. From this analysis, the applicant concludes that McCluskie et al. provides no motivation or suggestion to provide a better vector and that the skilled artisan would not have looked at McCluskie et al. to modify vector structure.

In response, it is first noted that applicant's portrayal of the KSR decision in incomplete. The Court concluded in KSR that while the TSM test is a valid rationale for determining obviousness in a 103 rejection, other rationales, not based on the TSM test, were also proper. The applicant is directed to MPEP 2143 and *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395-97 (2007). For convenience, a portion of MPEP 2143 is copied below.

> Exemplary rationales that may support a conclusion of obviousness include:
>
> (A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

Second, there is no requirement that McCluskie et al. provide motivation to modify the plasmid vector used in their methods let alone provide a specific suggestion to use a MIDGE vector as claimed. The rejection is based on the combined teachings of McCluskie et al. in view of Wittig et al. and Makkerh et al. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is also noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the

instant case, the rejection of record recognized that McCluskie et al. differs from the instant invention in that the DNA expression construct is a plasmid and in that the DNA is not covalently linked to an oligopeptide such as PKKKRKV. The rejection of record then cites Wittig et al. to supplement McCluskie et al. by teaching dumbbell shaped DNA expression constructs comprising covalently closed linear DNA that contains only a coding sequence operably linked to a promoter and polyA termination sequence where the linear ends are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to a peptide which directs transport of the construct across a cell's endosome or into the nucleus (Wittig et al., claims 1-11, and columns 5-8)). It was further pointed out that Wittig et al. specifically teaches the use of the nuclear localization sequence (NLS) from SV40, a sequence which inherently comprises PKKKRKV (Wittig et al., column 5). Wittig et al. also teaches a vaccine comprising this construct for treating infectious diseases (Wittig et al., columns 1 and 8). Wittig et al. was also cited for providing the motivation which the applicant argues is lacking in McCluskie et al. for using a dumbbell DNA expression construct linked to a peptide over a plasmid DNA expression construct. Wittig et al. teaches that because the dumbbell construct consists only of a promoter-gene-terminator sequence, these constructs have none of the disadvantages of plasmid constructs, which include their size, which inhibits fast transport into the cell's nucleus, and the presence of unwanted background sequences, including bacterial sequences, which can lead to unintended immune responses (Wittig et al., columns 2-3, bridging paragraph). Applicant's arguments, including the cited post-filing publication, corroborate the teachings of Wittig et al. as to the disadvantages of using a plasmid vector and add strength to the cited motivation in the rejection to use the dumbbell DNA expression construct (aka MIDGE

vector) taught by Wittig et al. instead of a plasmid vector as a vaccine. Thus, it is maintained that the skilled artisan reading Wittig et al. would find ample suggestion to substitute a MIDGE vector for a plasmid vector in the methods of McCluskie et al. to avoid all the disadvantages in using plasmid vectors argued by the applicants and taught by Wittig et al.

The applicant further argues that Wittig et al. and McCluskie et al. provide opposing teachings because McCluskie et al. only provide an incentive to modify a plasmid vector by adding CpG motifs, whereas the vector disclosed by Wittig et al. removes all the unnecessary sequence including the CpG motifs. In response, it is first noted that there is no page 259 in McCluskie et al., it is assumed that the applicant intended to refer to page 295. Second, McCluskie et al. on this page, discusses a number of different ways in which artisan in the field have attempted to improve DNA vaccine efficiency, of which adding additional CpG motifs is but one of 6 different variables listed. It is also noted that McCluskie et al. does not teach that the strategy of adding CpG motifs was successful or even the best approach, it is just one of many strategies mentioned in the article. Further, the fact that McCluskie et al. mentions one approach which the prior art has suggested to improve the efficacy of plasmid based vectors by adding CpG motifs does not teach away from using the motivation provided by Wittig et al. to substitute the use of a plasmid vector with a dumbbell (MIDGE) vector. As noted above, there is no requirement for McCluskie et al. to provide any teaching or suggestion to modify a plasmid vector to become a MIDGE vector, the teachings and motivation for using a MIDGE vector instead of a plasmid vector in a vaccine protocol is provided by Wittig et al.

Finally, the applicant argues that the linkage of a specific peptide as claimed is not obvious from Wittig et al. because Wittig et al. teaches three distinct peptides that could be

added to the expression construct and according to applicants there would have been uncertainty in applying any of these. The applicant also argues that the SV40 NLS is not a functional substitution but a non-obvious choice. In response, Wittig et al. provides a specific teaching to covalently link a peptide which directs transport of the construct across a cell's endosome or into the nucleus to the dumbbell construct, and further specifically teaches the use of the nuclear localization sequence (NLS) from SV40 (Wittig et al., column 5). The fact that two other NLS sequence were also taught to be useful does not raise any level of unpredictability concerning the use of the NLS from SV40, which is a well-known sequence. The applicant has provided no specific evidence of any uncertainty felt in the prior art over using the NLS from SV40 to target a construct to a nucleus. As such, it is maintained that the specific teaching of Wittig et al. to link the NLS from SV40 to a dumbbell construct useful as a vaccine is sufficient to provide a reasonable expectation of success in making such a construct and in using such a construct to elicit immune responses against hepatitis in a living being.

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The rejection of claim 43 under 35 U.S.C. 103(a) as being unpatentable over McCluskie et al. (1999) Mol. Med., Vol. 5, 287-300, (IDS of 7/04, ref AU), in view of U.S. Patent No. 6,451,593 (2002), effective filing date of at least May 12, 1999, hereafter referred to as Wittig et al. (of record), and Liu et al. (2001) Biomacromolecules, Vol. 2, 362-368 (of record), is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record.

The applicant reiterates their arguments regarding McCluskie et al. However, these arguments have been addressed in detail above and have not been found persuasive in overcoming the rejection. Therefore, the rejection of record stands.

Claims 42-44 are not allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center

fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

*/Anne Marie S. Wehbé/*
Primary Examiner, A.U. 1633